Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance.

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Authors: Sungsoon Fang, Jae Myoung Suh, Shannon M Reilly, Elizabeth Yu, Olivia Osborn, Denise Lackey, Eiji Yoshihara, Alessia Perino, Sandra Jacinto, Yelizaveta Lukasheva, Annette R Atkins, Alexander Khvat, Bernd Schnabl, Ruth T Yu, David A Brenner, Sally Coulter, Christopher Liddle, Kristina Schoonjans, Jerrold M Olefsky, Alan R Saltiel, Michael Downes, Ronald M Evans

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Public Summary:
The systemic expression of the bile acid (BA) sensor farnesoid X receptor (FXR) has led to promising new therapies targeting cholesterol metabolism, triglyceride production, hepatic steatosis and biliary cholestasis. In contrast to systemic therapy, bile acid release during a meal selectively activates intestinal FXR. By mimicking this tissue-selective effect, the gut-restricted FXR agonist fexaramine (Fex) robustly induces enteric fibroblast growth factor 15 (FGF15), leading to alterations in BA composition, but does so without activating FXR target genes in the liver. However, unlike systemic agonism, we find that Fex reduces diet-induced weight gain, body-wide inflammation and hepatic glucose production, while enhancing thermogenesis and browning of white adipose tissue (WAT). These pronounced metabolic improvements suggest tissue-restricted FXR activation as a new approach in the treatment of obesity and metabolic syndrome.

Scientific Abstract:
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